IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES

Appellants	:	MEYER et al.
Serial No.	:	10/569,714 (U.S. Patent Application Publication 2007-0077284)
Filing Date	:	21 September 2006
For	:	**TRANSDERMAL FORMULATION COMPRISING AN OPIOID ANALGESIC AND AN ALOE COMPOSITION**
Examiner	:	CHEN, Catherine
Art Unit	:	1655

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APPEAL BRIEF UNDER 37 C.F.R. 41.37

Mail Stop: Appeal Brief
Commissioner for Patents
P.O. Box 1450
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Sir:

This is an appeal filed in response to the Final Rejection of claims 1-3, 5 and 12-27 in the Office Action, dated 23 June 2010.

A Notice of Appeal had previously been filed on 27 April 2009 and therefore, no additional fee is believed to be required for the present Notice of Appeal. The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0320.

(I) REAL PARTY IN INTEREST

The real party in interest in this appeal is the assignee, Acino AG, who is the owner of this application by assignment from the inventor (Reel 022171/Frame 0536).

(II) RELATED APPEALS AND INTERFERENCES

Appellant is not aware of any related appeals or interferences which directly affect or are directly affected by or have bearing on the Board's decision in the pending appeal.

(III) STATUS OF CLAIMS

By the Office Action dated 23 June 2010, claims 1-3, 5 and 12-27 have been finally rejected. Claims 6, 28 and 29 are in withdrawn status.

Upon further review of the claims, claim 23 is dependent upon claim 6 which is in withdrawn status and therefore, claim 23 should also be in withdrawn status. Also, claim 24 is dependent upon claim 8 which was previously cancelled. Should the rejections be withdrawn or are reversed, and claim 24 is the only issue preventing allowance of the claims, the appellants authorize cancellation of claim 24 via an Examiner's Amendment.

Therefore, the proper status of the claims under Appeal is that claims 1-3, 5, 12-22 and 25-27 have been finally rejected and claims 6, 23, 28 and 29 are in withdrawn status.

(IV) STATUS OF AMENDMENTS

No amendments were filed after the final rejection of 23 June 2010 and it is believed that all other amendments have been entered.

(V) SUMMARY OF CLAIMED SUBJECT MATTER

The only independent claim under appeal is claim 1 which is directed to a transdermal formulation comprising a synthetic rubber adhesive selected from the group consisting of a styrene-butadiene-styrene block copolymer and a styrene-butadiene block copolymer, an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable salt thereof as active ingredient and an aloe composition as transdermal penetration agent.

Claim 1 under appeal is essentially the same as originally filed claim 1 which has been amended to include the elements of originally filed claims 6 and 8 (which represents the elected species for the adhesive). As all of the elements of claim 1 under appeal are present from the originally filed claims, claim 1 under appeal is supported by the specification. In addition, further support for the elements from originally filed claims 1, 6 and 8 are also found in the specification, e.g. page 4, line 11 through page 5, line 8.

(VI) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Claims 1-3, 5 and 12-14 were rejected as allegedly being obvious over Kleinsorgen (U.S. Patent 6,165,499).

B. Claims 1-3, 5 and 12-27 were rejected as allegedly being obvious over Kleinsorgen (U.S. Patent 6,165,499) as applied to claims 1-3, 5 and 12-14, further in view of Fischer et al. (U.S. Patent 6,455,066 – "Fischer").

The appellants note that a restriction/election of species requirement was mailed on 16 October 2010 and the appellants elected the following species:

Patch:	**matrix type patch**	
Adhesive:	**synthetic rubber**	
	Rubber adhesive:	**styrene-butadiene-styrene-block-copolymer**
Polyacrylate:	**polybutylacrylate**	
Penetration agent:	**N-methyl-pyrrolidone**	
Preservative:	**organic acids**	
Backing material:	**polyester**	

The election of species was never withdrawn and as such, the above elections represent the scope of the claims under appeal.

(VII) ARGUMENTS

Claims 1-3, 5, 12-14, 28 and 29 were rejected as allegedly being obvious over Kleinsorgen et al. (U.S. Patent 6,165,499 - Kleinsorgen).

In order to establish *prima facie* obviousness, all claim limitations must be taught or suggested by the prior art reference or be within the knowledge of those of ordinary skill in the art. *See MPEP 2143.03.* In addition, because of the restriction requirement, any reference which

fails to teach any of the elected elements described above, would be considered to be a patentably distinct invention. *See MPEP 806.04(h).*

1. Obvious to try rationale for the generic teaching of Kleinsorgen does not apply to the specific invention claimed by the appellants

The final rejection of 23 June 2010 ("the final rejection) refers to generic recitations of elements for the appellants claimed invention (see page 3, lines 3-16 of the final rejection). However, the final rejection also acknowledges that Kleinsorgen does not teach all of the appellants' claimed elements in simultaneous combination (see page 3, line 17).

Moreover, for the invention as examined, there has been no indication that the restriction/election of species has been withdrawn or that the scope of the examination was expanded beyond the appellants' elected species, the invention was presumed to be examined for the election wherein:

1. The patch is a matrix-type patch
2. The adhesive is a synthetic rubber which in turn is comprised of styrene-butadiene-styrene block copolymer
3. The another penetration enhancer is an N-methyl pyrrolidone
4. The preservative is an organic acid
5. The backing comprises of polyester.

As such, by virtue of the restriction/election of species requirement, this election was deemed to be patentably distinct from other elections which could have been made by the appellants.

In addition, even the originally filed claims were limited to a specific type of active ingredient, i.e. an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable thereof, and a specific type of transdermal penetration agent, i.e. an aloe composition.

It has long been held that "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." (see *In re Wesslau*, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965)).

More recently, the PTO's own Examination Guideline Update (see Fed. Reg., vol. 75, No. 169, September 1, 2010) quotes from *Rolls-Royce* that "an obvious to try rational may be

proper when the possible option for solving a problem were known and finite. However, if the possible options were not either known or finite, then an obvious to try rationale cannot be used to support a conclusion of obviousness." *See Rolls-Royce, PLC v. United Technologies Corp.*, 603 F.3d 1325 (Fed. Cir. 2010). To hold otherwise would simply preclude the patentability of virtually any pharmaceutical composition by simply reciting a generic text (e.g. Remington's Pharmaceutical Sciences in combination with The Merck Index).

Applying this framework to Kleinsorgen, it should be apparent to one of ordinary skill in the art that Kleinsorgen is not even directed to the combination of an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable thereof and an aloe composition much less the other elements of the appellants' claimed transdermal formulation.

When considering the Kleinsorgen reference as a whole, it is clear that Kleinsorgen is directed toward the therapeutic system itself, i.e. a system comprising a substrate (1) provided with a separating layer (2), a film layer (3) comprising the active substance, and a protective layer (4) provided with a non-stick finish, the separating layer (2) consisting of a material whose bond to the film layer (3) may be abolished, i.e. the solution to the problem lies in the elements of Kleinsorgen's system not the active ingredients which can be part of the system. *See* Abstract.

There is no teaching or direction for the specific combination of opioid analgesic and aloe composition from with Kleinsorgen as the reference makes broad recitations to "transdermally applicable active substances" (see col. 5, line 44 – col. 6, line 17). This alone would not render the appellants claim to be obvious over Kleinsorgen as this does not represent a finite number of solutions to the problem to be solved and as noted earlier, selection of the appropriate active substance is not even the problem Kleinsorgen is trying to solve.

When considering that one of ordinary skill in the art must also select an aloe composition in combination with the opioid analgesic, the logic for obviousness is even more remote especially given the fact that within Kleinsorgen, aloe vera is merely one of many possible vegetable preparation which can be used and the fact that the use of a vegetable preparation is an optional element within the teaching of Kleinsorgen (see col. 6, lines 18-49).

In addition to referring to virtually an infinite number of potential active agents, Kleinsorgen only refers to aloe vera extract in the context of Kleinsorgen's film layer comprising a vegetable preparation, not within the context of being a transdermal penetration agent. While the rationale for combination does not have to be the same as the appellants', not only is there no

direction from the virtually infinite possible combination of active agents and vegetable preparations, even if one of ordinary skill in the art had been directed to select an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable thereof and an aloe composition, there is no evidence that using an aloe vera extract in Kelinsorgen's film layer would have resulted in transdermal penetration.

Furthermore, one of ordinary skill in the art having to specifically choose other elements to meet the criteria of the appellants' claims, e.g. synthetic rubber adhesive, styrene-butadiene-styrene block copolymer, matrix type patch (claim 3), N-methyl-pyrrolidone as an additional penetration agent (claim 18), an organic acid as a preservative (claim 19), it is clear that the artisan is not confronted with a known and finite number of solutions for transdermal delivery of an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable thereof.

Lastly, the reliance on the case law recited on page 3, last paragraph through page 4 of t he final rejection is misplaced. MPEP 2144.04 states that "...if the facts in a prior legal decision are sufficiently similar to those in an application under examination, the examiner may use the rationale used by the court." However, the facts surrounding this application is not similar to the facts of the case law cited by the Examiner.

In re Kerkhoven is representative of the case law relied upon. In this decision, it was held that the combination of two detergent compositions to form a third detergent composition would have been obvious. In contrast, in the present situation, the transdermal compositions of Kleinsorgen are different than those claimed by the appellants. Not only does Kleinsorgen not teach the specific combination of elements described in the appellants' claims, but the entire structure of Kleinsorgen's transdermal devices are different.

Kleinsorgen refers to decals for transdermal use and also refers to "[a] soluble separating layer [which] is applied on a substrate...Differentiation of this laminate film into two individual layers may be supported by a barrier layer which prevent components from reaching the substrate during application. A capillary active insoluble substrate provided with a soluble separating layer ***is essential***." (see col. 3, lines 19-27 of Kleinsorgen)(emphasis added). This is clearly not the same type of transdermal composition claimed by the appellants which lends itself modification in the manner claimed by the appellants or for combination with another transdermal composition.

Therefore, Kleinsorgen fails to teach or suggest all of the limitations of the appellants' transdermal formulations.

2. Appellants provided evidence of secondary considerations which further established that the claimed transdermal formulation was unobvious over Kleinsorgen

When considering the appellants invention as a whole, the present invention provides a solution for the problem of imparting a pharmaceutical formulation with properties which enable an opioid analgesic to be transdermally administered. The solution for this problem consists of

- a transdermal formulation comprising
- a synthetic rubber adhesive selected from a styrene-butadiene-styrene block copolymer or a styrene-butadiene block copolymer,
- an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable salt thereof as active ingredient and
- an aloe composition as transdermal penetration agent.

With respect to claim 1 under appeal, the formulation comprises a synthetic rubber adhesive selected from a styrene-butadiene-styrene block copolymer or a styrene-butadiene block copolymer.

The inventors carried out comparative experiments which are similar to Example 1 in the specification and which were presented in the Declaration by Dr. Elisabeth Meyer (Exhibit A – first presented with the response filed on 27 August 2009).

In Example 1 of the description of the present application experiments with different matrix patches are presented. The results are summarized in Table I on page 16 of the description. A matrix patch is provided which comprises a mixture of buprenorphine (the analgesic), an aloe (the transdermal penetration agent) and a styrene-butadiene-styrene polymer (the adhesive). Flux experiments with hairless mouse skin reveal buprenorphine fluxes in the range from 0.8 to 2.3 $\mu g/cm^2*h$ and the transdermal penetration effect of aloe compositions.

In the comparative experiments, the styrene-butadiene-styrene polymer (the adhesive) was replaced by several acrylate adhesives, i.e. the adhesive which is disclosed by Fischer as the usual adhesive in combination with the intradermal penetration agent (the aloe composition) and the drug.

The results as disclosed in the description and the results of the comparative experiments are presented in the following table below:

Adhesive type	PSA	Buprenorphine (% w/w)	*Aloe vera* (% w/w)	Flux (hairless mouse skin)	**Formation of crystals**
Examples of the Present Invention (cf. Table I of the invention, page 16)					
Styrene-butadiene-styrene polymer	DT 6173	15	20	2.3 µg/(cm^2*h)	–
Styrene-butadiene-styrene polymer	DT 6173	5	20	0.8 µg/(cm^2*h)	–
Styrene-butadiene-styrene polymer	DT 6173	10	10	0.9 µg/(cm^2*h)	–
Comparative Examples					
Acrylate-vinylacetate with carboxy groups	DT 2825	10	10	1.1 µg/(cm^2*h)	+
Acrylate-vinylacetate with hydroxyl groups	DT 2287	10	10	1.1 µg/(cm^2*h)	+
Acrylate with functional hydroxy groups	DT 2510	10	10	1.3 µg/(cm^2*h)	+
Acrylate-vinylacetate without functional groups	DT 4098	10	10	1.5 µg/(cm^2*h)	+

It should first be noted that in the original description of the present application the fluxes are accidentally given as g/(cm^2*h). In fact, also in the case of the invention the fluxes are in the micro gram range and should read as µg/(cm^2*h) which was corrected in the specification with the response filed on 27 August 2009.

When comparing the results of the above experiments in which the patches comprise 10 % (w/w) *Aloe vera* it turns out that the fluxes which are obtained with the styrene-butadiene-styrene polymers as adhesive (according to the invention) and with the acrylates as adhesives (comparative examples) are similar. ***However, with the acrylate polymers a disadvantageous crystallization of the drug (buprenorphine) in the matrix is observed over the time.*** Such a crystallization reduces the long term stability of the formulations and the amount of drug available for the transdermal penetration is very disadvantageous for transdermal applications, for which a relatively high concentration of the dissolved drug in the pharmaceutical formulation is needed. This disadvantageous crystallization effect can be avoided using the styrene-butadiene-styrene polymers of the invention.

3. Determination of obviousness must also consider the effect of the restriction requirement and dependent claims

As the restriction requirement is still in force, the application under examination is for a formulation which must have the elements that the (1) patch is a matrix-type patch; (2) the adhesive is a synthetic rubber which in turn is comprised of styrene-butadiene-styrene block copolymer; (3) the another penetration enhancer is an N-methyl pyrrolidone; (4) the preservative is an organic acid; and (5) the backing comprises of polyester.

In addition to the deficiencies of Kleinsorgen mentioned above, there is nothing which suggests that Kleinsorgen has a transdermal system which simultaneously has all five of these elements. Furthermore, the restriction requirement is prima facie evidence than any element missing from these five elected elements constitutes a patentably distinct invention.

Lastly, claim 12 is directed toward a specific opioid analgesic, i.e. buprenorphine, the specificity of which is even less obvious given the virtually infinite number of potential compounds which could be used as an active agent within Kleinsorgen.

4. Conclusion

Any of the above reasons alone establish that Kleinsorgen does not render the appellants' claimed invention to be obvious and when considered collectively, Kleinsorgen is far removed from establishing a *prima facie* case of obviousness and therefore, this rejection may be withdrawn.

Claims 1-3, 5 and 12-29 were rejected as allegedly being obvious over Kleinsorgen et al. (U.S. Patent 6,165,499 - Kleinsorgen) as applied to claims 1-3, 5, 12-14, 28 and 29 in view of Fischer et al. (U.S. Patent 6,455,066 – "Fischer")

Fischer is being relied upon in combination with Kleinsorgen presumably to address claims 15-27. As claims 15-27 are either directly or indirectly dependent upon claims 1-3, 5, 12-14, 28 and 29 which the appellants have established is not obvious in view of Kleinsorgen, claims 15-27 are also unobvious in light of Kleinsorgen and Fischer. However, the appellants provide further comments as to why the combination of Kleinsorgen and Fischer does not render claims 15-27 obvious.

As earlier noted, the appellants' invention is directed toward a ***transdermal*** formulation whereas the invention of Fischer is directed toward an ***intradermal*** composition. The differences

in administration is well known in the art and is even addressed by Fischer themselves in the background of their invention (see col. 1, lines 39-48).[1] As one of ordinary skill in the art would recognize that intradermal administration is intended to ***avoid*** any transdermal absorption, the Fischer reference would not be readable upon or suggestive of the appellants' transdermal formulation nor would be recognizable by one of ordinary skill in the art to be relevant for combination with a reference which is directed to transdermal systems such as Kleinsorgen.

The appellants previously explained the differences between intradermal and transdermal delivery in their response filed on 27 August 2009.[2]

Intradermal administration is the transportation of a drug into the skin, more specifically, into the dermis, **without the uptake into the venules and arterioles**, which only populate the deeper layers of the skin, i.e. the hypodermis. See page 145 from *Concepts of Human Anatomy and Physiology*, Wm. C. Brown Publishers, (1992) – (Exhibit C) which is attached to this response which includes a diagram of the integumentary system (skin).

In other words, the drug penetrates from the vehicle (e.g. in a patch) through the *Stratum corneum* into the epidermis and possibly into the dermis, however without reaching the capillaries and the blood stream in a pharmacologically relevant amount. Intradermal administration thus serves for the topical administration of a drug which should be effective in the skin. An example for these drugs are anesthetics. Intradermal administration is intended to impart a cutaneous effect. Intradermal absorption occurs with little or no systemic absorption.

In contrast, **transdermal administration** includes necessarily all of the above described aspects of intradermal administration. However, in the case of transdermal administration, the further transportation of the drug in the vicinity of the capillaries and the uptake of the drug by the blood capillaries are desired, i.e. into the hypodermis. An example for these drugs are

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[1] "In general, drug administration via the skin is divided into two categories: 1) ***transdermal*** administration and 2) ***intradermal*** administration. Transdermal administration involves transport through the skin and into the blood stream to treat systemic diseases. One the other hand, intradermal administration is intended to impart a cutaneous effect, while keeping the pharmocological effects of the drug localized to the intracutaneous regions of drug penetration and deposition. ***Ideally, intradermal absorption occurs with little or no systemic absorption or accumulation.***" (emphasis added)

[2] The appellants attach to this response further evidence of the differences between intradermal and transdermal delivery from Allen et al., *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (8th Edition)*, pages 298 and 448, (2005) – (Exhibit B). – "Transdermal drug delivery systems (TDDSs) facilitate the passage of therapeutic quantities of drug substances ***through the skin*** and ***into the general circulation for their systemic effects***. pg. 298 (emphasis added). "A number of substances may be effectively injected into the corium [the dermis], the more vascular layer of the skin just beneath the epidermis. These substances include various agents for diagnostic determinations, ***desensitization***, or immunization." pg. 448 (emphasis added).

analgesics. Transdermal administration is intended to impart a systemic effect. Transdermal absorption occurs predominantely with systemic absorption into the arterioles and venules, after the absorption into the skin has occurred.

Therefore, the Examiner's statement is factually incorrect as intradermal administration does NOT occur after transdermal delivery. Intradermal administration speaks to an administration method which is different and distinct from transdermal administration and is even recognized as such within the Fischer reference (see again col. 1, lines 39-48).

In addition, Fischer is directed toward the delivery of an ***anesthetic*** whereas the appellants' transdermal formulation is directed toward delivery of an ***opioid analgesic*** from the phenanthrene group which is consistent with their disclosed methods of delivery, i.e. Fischer wants localized delivery of their anesthetic and to avoid systemic delivery whereas the appellants' invention wants to provide systemic delivery to maximize the pain relief associated with the opioid analgesic.

Moreover, Fischer recognized that the behavior of a penetration enhancer is strongly dependent on the drug (see col. 2, lines 35-41) and as such one of ordinary skill in the art would not impute the penetration activity of aloe vera with an anesthetic as being predictive of the activity with an opioid analgesic and in this instance, it is uncertain what relevance of such predictability would be as Fischer and the appellant are directed toward inventions with opposite modes of action.

Third, Fischer also lacks a teaching for some of the elected features of the appellants' claimed invention, i.e. Fischer does not teach a matrix-type patch or that the adhesive is a synthetic rubber which in turn is comprised of styrene-butadiene-styrene block copolymer.

The appellants further add that Fischer is silent as to the adhesive being comprised of styrene-butadiene-styrene block copolymer.

For these reasons, the combination of Kleinsorgen and Fischer does not render any of the appellants' pending claims to be obvious.

(VIII) CLAIMS APPENDIX

1. (Previously presented) Transdermal formulation comprising

a synthetic rubber adhesive selected from the group consisting of a styrene-butadiene-styrene block copolymer and a styrene-butadiene block copolymer,

an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable salt thereof as active ingredient and

an aloe composition as transdermal penetration agent.

2. (Previously presented) Formulation according to claim 3, wherein the patch is provided with a covering layer.

3. (Previously presented) Formulation according to claim 1, wherein the formulation is a patch selected from the group of matrix type patch, reservoir type patch, multi-laminate drug-in-adhesive type patch, and monolithic drug-in-adhesive type patch.

4. (Cancelled)

5. (Previously presented) Formulation according to claim 3, wherein the patch comprises a backing, and a release liner.

6. (Previously presented - withdrawn) Formulation according to claim 1, further comprising an adhesive selected from the group consisting of natural rubber; acrylic adhesive; polyvinylacetate; polydimethylsiloxane; hydrogels, high molecular weight polyvinlpyrrolidone and oligomeric polyethylene oxide.

7-11. (Cancelled)

12. (Previously presented) Formulation according to claim 1, wherein the analgesic is buprenorphine or a pharmaceutically acceptable salt thereof.

13. (Previously presented) Formulation according to claim 1, wherein the extracting agent of the aloe extract or the vehicle is a vegetable oil.

14. (Previously presented) Formulation according to claim 12, wherein the extracting agent of the aloe extract or the vehicle is a vegetable oil.

15. (Original) Formulation according to claim 14, wherein the vegetable oil is hydrogenated oil.

16. (Previously presented) Formulation according to claim 14, wherein the vegetable oil is soybean oil.

17. (Previously presented) Formulation according to claim 1, wherein the formulation comprises another penetration agent in addition to the aloe composition.

18. (Previously presented) Formulation according to claim 17, wherein the additional penetration agent is selected from the group consisting of ethyl alcohol; isopropyl alcohol; octyl phenol; polyethylene glycol octylphenyl ether; oleic acid; poyethyline glycol (PEG), PEG 400; propylene glycol; N-decylmethyl sulfoxide; fatty acid esters, isopropyl myristate, methyl laurate, glycerol monooleate, propylene glycol monooleate; and N-methyl pyrrolidone.

19. (Previously presented) Formulation according to claim 1, wherein the formulation comprises a preservative selected from the group of alcohols, quaternary amines, organic acids, parabens and phenols.

20. (Previously presented) Formulation according to claim 5, wherein the backing comprises of a material selected from the group consisting of polyolefin, polyester, polyvinylidene chloride, polyurethane, cotton or wool.

21. (Original) Formulation according to claim 20, wherein the backing is a polyolefine foil.

22. (Original) Formulation according to claim 21, wherein the foil has a thickness of 0.5 to 1.5 and especially 0.6 to 1.0 mm.

23. (Previously presented) Formulation according to claim 6, wherein the adhesive consists of a component selected from the group of natural rubber; synthetic rubber; acrylic adhesive; polyvinylacetate; polydimethylsiloxane; hydrogels, high molecular weight polyvinlpyrrolidone and oligomeric polyethylene oxide.

24. (Previously presented) The formulation of claim 8, wherein the rubber adhesive consists of a styrene-butadiene-styrene block copolymer or a styrene-butadiene block polymer.

25. (Previously presented) The formulation of claim 20, wherein the formulation comprises a backing consists of a material selected from the group consisting of polyolefin, polyester, polyvinylidene chloride, polyurethane, cotton or wool.

26. (Previously presented) Formulation according to claim 13, wherein the vegetable oil is hydrogenated oil.

27. (Previously presented) Formulation according to claim 13, wherein the vegetable oil is soybean oil.

28. (Previously presented - withdrawn) A method of enhancing the penetration of a formulation comprising an opioid analgesic from the phenanthrene group which comprises of adding an aloe composition to said formulation to form the formulation of claim 1.

29. (Previously presented - withdrawn) A method of transdermally administering an opioid analgesic from the phenanthrene group which comprises of applying the formulation of claim 1 to the skin of patient in need thereof.

(IX) EVIDENCE APPENDIX

EXHIBIT A - Declaration by Dr. Elisabeth Meyer - first filed on 27 August 2009

EXHIBIT B – Eds. Allen et al., *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems* (Eighth Edition), pages 298 and 448 (2005) – first filed on 27 August 2009 as part of RCE.

EXHIBIT C – *Concepts of Human Anatomy and Physiology* (Third Edition), pg. 145 (1992) – first filed on 27 August 2009 as part of RCE.

(X) RELATED PROCEEDINGS APPENDIX

None

CONCLUSION

In view of the foregoing, it is respectfully submitted that the claims on appeal are patentable and that the rejection under 35 U.S.C. §103(a) should be reversed.

Respectfully submitted,

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